Therapeutic Effect of Sentinel Lymph Node Biopsy in Melanoma Remains an Open Question

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BACKGROUND

Whether sentinel lymph node biopsy (SLNB) in melanoma improves survival remains an open question. During the past two decades there have been five randomized controlled trials (RCTs) investigating the therapeutic effect of dissection of clinically uninvolved regional lymph nodes at the time of definitive surgery at the primary site. Four of these RCTs¹⁻⁴ examined the impact on disease-specific survival of having a prophylactic lymph node dissection (PLND; Table 1). In all but one of these RCTs there was no evidence in the primary analyses of a survival benefit for those who received PLND. The fourth trial³ demonstrated a significant effect—the survival rate was 62% among those who received PLND compared with 51% in those who did not. One explanation for the disagreement among these trials is differences in their inclusion criteria that resulted in target populations with important differences in key prognostic factors. For example, in the only trial that demonstrated a significant therapeutic effect the target population (men with axial melanomas) was characterized by substantially poorer prognostic factors compared to the patients in the other trials.

The only RCT of SLNB—the Multicenter Selective Lymphadenectomy Trial (MSLT)—was designed to evaluate the therapeutic

benefit of the procedure in patients with intermediate thickness melanomas.⁵ MSLT enrolled 1,269 such patients between 1994 and 2002. In this trial, 769 patients were randomly assigned to receive SLNB, with immediate lymphadenectomy if nodal micrometastases were detected, and 500 were randomly assigned to observation, with subsequent lymphadenectomy if nodal relapse occurred. The effect size for the difference in 5-year survival rates corresponding to 80% power for the sample sizes in this clinical trial can be computed. Assuming 5-year melanoma-specific survival rates of 50% to 90% in the control group, the corresponding effect sizes for 5-year melanoma-specific survival rate would be 8.2% to 4.5%, corresponding to odds ratios of 1.4 to 1.9. In the report of the trial's primary outcome, based on data where all patients had at least 5 years of follow-up, the 5-year disease-free survival rates were identical (87% for both groups). These results contradicted the belief held by some in the melanoma community that SLNB would improve patient survival, particularly in those patients with primary tumors of intermediate risk, those who were eligible for the MSLT. However, before concluding that the intervention had no effect on survival, it is worth considering two challenges to the validity of this finding. These relate to issues of power and bias. The power calculations above demonstrate that the sample size for this trial was insufficient to detect a small but clinically relevant (eg, 5%) survival difference between the two treatment groups when the 5-year survival rate in the control group was lower than 88%. Further, there is some evidence for bias since the 5-year survival rate for those randomly assigned to the control group (87%) was higher than expected for comparable populations (eg, 81% for SEER patients diagnosed in 1994 to 1995 who would have met the MSLT inclusion criteria or 80% for patients in the historical control group from the John Wayne Cancer Institute that was used in designing the MSLT; D.L. Morton, personal communication, April 2009).

Alternative Approach to the Question

We sought to contribute to the ongoing discussion of whether or not SLNB has a survival benefit by conducting an observational study that included patients who met the eligibility criteria of the MSLT. We hypothesized that we would validate the results of the

Table 1. Summary of Randomized Controlled Trials

Study	Survival Rate				% Extremity Male	
	Procedure		No Procedure			
	No.	%	No.	%		
Prophylactic lymph node dissection						
Veronesi (5 year) ¹	267	74	286	74	100	17
Sim (5 year) ²	54	89	56	86	100	35
Cascinelli (5 year) ³	128	62	124	51	0	65
Balch (10 year) ⁴	379	77	361	73	48	50
SLNB						
MSLT (5 year)	769	87	500	87	47	57

Abbreviations: SLNB, sentinel lymph node biopsy; MSLT, Multicenter Selective Lymphadenectomy Trial.

MSLT and find no benefit. Publically available data from the National Cancer Institute's cancer registry, Surveillance Epidemiology and End Results (SEER) between 1998 and 2002 provided the data for this investigation.⁶

In this study, the inclusion criteria of the MSLT's target population (patients with primary melanomas 1.2 to 3.5 mm in thickness who were 18 to 75 years old) were used and 674 matched pairs of patients (one patient with and one without SLNB) were identified using propensity scores⁷ to control for important selection biases and distance matching⁸ to control for prognostic factors. The only factors used in the matching were those known before the SLNB (sex, age at diagnosis, anatomic site, Breslow thickness, Clark level, ulceration, histopathologic type, and year of diagnosis). In our presentation of this study,⁹ we answered the question of the therapeutic efficacy of SLNB in the affirmative, challenging the MSLT results. However, during the session discussion a member of the audience raised a question about previously unreported coding problems in SEER that resulted in information about the occurrence of SLNB being inaccurately recorded from 1998 to 2002.

The SEER coding manual¹⁰ for melanoma procedures during this time said: "The codes are hierarchical. If only one procedure can be recorded, code the procedure that is numerically higher." The implication of this coding algorithm for melanoma patients was that if the SLNB was followed by a completion regional lymph node dissection (RLND), then the RLND was to be noted, but not the SLNB that preceded it. Of note and in contrast, the coding algorithm for nodal procedures in patients with breast cancer differed and distinctly characterized four groups of patients, those who had no procedure, SLNB only, SLNB and RLND, and RLND only.

Having examined the matter in some detail, we agree that the concern is valid, at least in part, and we have concluded that the SEER data for 1998 to 2002 reflect both correct and incorrect coding by the faulty algorithm mentioned above. Patients with melanoma who were coded as having SLNB were ostensibly only those with no regional nodal metastasis. However, there appeared to be some anomalies in the SLN data in SEER with there being a higher than expected percentage of patients with positive regional nodes who did not appear to have a RLND. In our main analysis, the SLNB patients matched were identified from a pool of 1,063 patients who were recorded as having had SLNB. We found 8.5% of these patients were recorded as having 1 or more positive lymph nodes (this rate should have been 0, if coding followed the algorithm and all patients with a positive SLN went on to a completion RLND). The observed SEER SLN positivity rate was indeed lower than the 16% observed in otherwise comparable patients reported in the MSLT, whose criteria for patient selection we used.³ Based on the rules for coding melanoma procedures, either these patients with positive SLNBs did not go on to completion RLND or these patients were incorrectly coded.

As a consequence of the faulty coding algorithm for melanoma procedures, our SLNB group was likely enriched with patients in whom the SLNB was negative, while perhaps including some patients in whom SLNB was positive and the RLND was negative. After extensive evaluation, we believe that the uncertainty in the interpretation of these data invalidate the results reported in our abstract (ie, that the SEER-based data presented in the abstract

provides evidence for a therapeutic effect of SLNB among patients similar to those enrolled in MSLT).

CONUNDRUM

The MSLT demonstrated that SLNB outcomes in patients with intermediate thickness melanomas have staging and prognostic value, but it left open the question of a survival benefit. It is unlikely that a larger, population-based RCT will be done to address this issue. It is in this circumstance (among others) that an observational study has the potential to provide useful information. We have continued to investigate the prognostic impact of SLNB with data collected for SEER patients who had characteristics similar to the patients in the MSLT and who were diagnosed during the period 2003 to 2005, when the SEER coding conventions were revised to clearly indicate which patients had SLNB. However, we were not able to design the same study using matched pairs of patients with intermediate melanomas for two main reasons. First, the SLNB has become so routine in recent years that differences between those who receive and those who do not receive the SLNB are more substantial and not easily adjustable by the methods in our previous study, and there are fewer patients without SLNB to form pairs, thus reducing the power of the study. Second, with only SEER 2005 data then available, the patients diagnosed in 2003 to 2005 have too little follow-up time for testing meaningful survival end points such as 5-year disease-specific rates.

Given these considerations, we believe that information on SLNB for SEER patients diagnosed between 1998 and 2002 is critically important for its unique potential to provide information about the therapeutic effect of SLNB. We have proposed to the SEER program a plan to obtain accurate data on the use of SLNB in these patients. Unfortunately, it has been deemed too expensive to correct these data. We believe that this decision should be reconsidered, both to justify the faith of investigators, policy makers, and the public in the veracity of SEER data generally and to answer the specific question of the impact of SLNB on survival in melanoma patients. For the present, clinicians discussing with their patients the pros and cons of SLNB should not use the data in our abstract to argue for a direct and beneficial effect on survival of the procedure.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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